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GENITAL TALC EXPOSURE AND RISK OF OVARIAN CANCER

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Epidemiologic studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene, but the biologic credibility of the association has been questioned. We conducted a population-based case-control study in eastern Massachusetts and New Hampshire involving 563 women with newly diagnosed epithelial ovarian cancer and 523 control women selected either by random digit dialing or through lists of residents. Use of body powders was assessed through personal interview and the exposure odds ratio (OR) for the use of talc in genital hygiene was calculated. Cases were more likely than controls (45% *vs.* 36%) to have used talc as a body powder in some manner, and the excess was confined to patients who used talc on the perineum directly or as a dusting powder to underwear or sanitary napkins. Relative to women who never used body powder or used it only in non-genital areas, the OR (and 95% confidence interval) associated with genital exposure to talc was 1.60 (1.18 and 2.15) after adjustment for age, study location, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. Exposure prior to rather than after a first livebirth appeared to be more harmful, and the association was most apparent for women with invasive serous cancers and least apparent for those with mucinous tumors. We conclude that there is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer that, when viewed in perspective of published data on this association, warrants more formal public health warnings. *Int. J. Cancer* 81:351–356, 1999.
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An association between the use of talc in genital hygiene and ovarian cancer was first examined in an epidemiologic study in 1982 (Cramer *et al.*, 1982). An elevated odds ratio for genital talc exposure was observed in this study, in 8 of the largest subsequent epidemiological studies (Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow *et al.*, 1992; Chen *et al.*, 1992; Purdie *et al.*, 1995; Shushan *et al.*, 1996; Cook *et al.*, 1997; Chang and Risch, 1997) and in a study of borderline tumors (Harlow and Weiss, 1989). Only 3 smaller studies reported a null association (Hartge *et al.*, 1983; Rosenblatt *et al.*, 1992, Tzonou *et al.*, 1993). Despite this consistency, the association is still viewed with skepticism based upon weak odds ratios, poor dose-response relationships and an incomplete understanding of the biological mechanism by which talc might lead to ovarian cancer. We have completed a large population-based case-control study of ovarian cancer which offers new perspectives on the validity of the talc and ovarian cancer association.

MATERIAL AND METHODS

We conducted a population-based case-control study of women with newly diagnosed ovarian cancer who resided in eastern Massachusetts (MA) or New Hampshire (NH). Women with ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Between 5/92 and 3/97, 1,080 cases of ovarian cancer were identified. After excluding 203 cases who had died or moved, had no telephone, did not speak English or had a non-ovarian primary tumor after review, 877 women remained eligible. Physicians denied permission to contact 126 (14%) of these women, and 136 cases (16%) declined to participate. Our analysis is based upon data from 563 cases with epithelial ovarian cancer, including those with tumors of borderline malignancy.

We identified control women using random digit dialing (RDD) in which the sampling unit for an interviewed case comprised the 99 telephone numbers generated from the first 5 digits of her telephone number plus all remaining combinations of the last 2 digits (excluding the case's own number). These numbers were listed in random order and called to screen households for potential controls who were within 4 years of the age of the case. Excluding business and non-working numbers, approximately 5,400 calls yielded 10% of households in which the household member declined to provide a household census and 80% of households in which an age and sex matched control for a case could not be made or a potential control was ineligible because of a prior oophorectomy. Of the remaining 10% of households screened with a potential eligible control, 72% agreed to participate. RDD proved inefficient for identifying controls over age 60 in MA since a substantially greater number of households needed to be screened to obtain an older control. Except in NH where complete listings of residents were unavailable, we chose to identify older controls in MA by randomly selecting women through use of lists (townbooks) of all residents in towns by name, age, and address according to precinct. We matched older controls to cases by community and age within 4 years based on the townbooks. Of 328 sampled townbook controls, 21% could not be reached, 18% were ineligible and 30% declined to participate. This analysis includes a total of 523 RDD and townbook controls.

In introducing the study to potential cases and controls, specific hypotheses including the talc association were not discussed. After written informed consent, we assessed demographic information, menstrual and reproductive history, medical and family history and personal habits using an in-person interview. We assessed exposures occurring prior to a "reference date," defined as 1 year before the date of diagnosis for cases and the date of interview for controls. We asked whether women had "regularly used talc, baby, or deodorizing powders dusted or sprayed" to feet, arms or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear, with the latter 3 methods defined as "genital exposure" and either no use or use in non-genital areas defined as "no genital exposure." A husband's use of powder in his genital area was also assessed. Age at first use, types of powder(s) used, applications per month and total years of use in genital hygiene were assessed in talc users. We did not assess potential talc exposure from diaphragms or condoms, exposures not found to be associated with ovarian cancer in our previous studies (Cramer *et al.*, 1982; Harlow *et al.*, 1992).

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TABLE I – PERINEAL TALC EXPOSURE[1] IN RELATION TO OVARIAN CANCER RISK BY CHARACTERISTICS OF STUDY PARTICIPANTS

	Cases		Controls		Age-adjusted[2] OR	(95% C.I.)
	Total	Talc exposure (%)	Total	Talc exposure (%)		
Age						
<50	266	66 (24.8)	262	43 (16.4)	1.68	(1.09, 2.58)
≥50	297	86 (29.0)	261	52 (19.9)	1.64	(1.11, 2.43)
Study center						
MA	433	126 (29.1)	411	85 (20.7)	1.56	(1.14, 2.14)
NH	130	26 (20.0)	112	10 (8.9)	2.49	(1.14, 5.45)
Education						
≤12	218	58 (26.6)	171	28 (16.4)	1.79	(1.08, 2.97)
>12	344	93 (27.0)	352	67 (19.0)	1.59	(1.10, 2.27)
Marital status						
Never married	110	31 (28.2)	61	10 (16.4)	1.77	(0.78, 4.00)
Ever married	453	121 (26.7)	462	85 (18.4)	1.62	(1.18, 2.22)
Religion						
Jewish	54	18 (33.3)	44	10 (22.7)	1.69	(0.68, 4.18)
Non-Jewish	509	134 (26.3)	479	85 (17.8)	1.63	(1.20, 2.22)
Weight						
<140	237	57 (24.0)	247	40 (16.2)	1.60	(1.02, 2.53)
≥140	326	95 (29.1)	275	55 (20.0)	1.65	(1.13, 2.42)
Use of OCs (months)						
<3 or never	334	98 (29.3)	247	52 (21.0)	1.55	(1.06, 2.28)
≥3	229	54 (23.6)	276	43 (15.6)	1.67	(1.07, 2.61)
Number of liveborn children						
0	185	55 (29.7)	106	20 (18.9)	1.65	(0.92, 2.98)
1–2	212	49 (23.1)	209	34 (16.3)	1.56	(0.95, 2.54)
3+	166	48 (28.9)	208	41 (19.7)	1.69	(1.04, 2.75)
Prior tubal ligation						
No	488	135 (27.7)	437	76 (17.4)	1.80	(1.31, 2.47)
Yes	75	17 (22.7)	86	19 (22.1)	0.98	(0.46, 2.08)
Prior hysterectomy						
No	529	139 (26.3)	487	88 (18.1)	1.60	(1.18, 2.16)
Yes[3]	34	13 (38.2)	36	7 (19.4)	2.61	(0.88, 7.78)
Family history of breast or ovarian cancer						
No	481	132 (27.4)	462	87 (18.8)	1.59	(1.17, 2.17)
Yes	82	20 (24.4)	61	8 (13.1)	2.21	(0.89, 5.48)

OR: odds ratio; CI: confidence interval; OCs: oral contraceptives.–[1]Sources of perineal talc exposure include dusting of underwear, diaphragms, sanitary napkins and/or dusting of genital area.–[2]Adjusted for age as a continuous variable.–[3]Excludes those with tubal ligation prior to hysterectomy.

For all cases studied, we reviewed pathology reports and sought slides in any instance where there was a discrepancy between histologic description and final diagnosis. After completing the review, cases were grouped according to the following histologic categories: serous cancers (including serous cystadenocarcinomas and surface papillary carcinomas), mucinous cancers, endometrioid and clear cell cancers, including mixed mesodermal or mixed epithelial with an endometrioid or clear cell component) and undifferentiated or other cancers. According to Young *et al.* (1994), serous tumors tend to be either borderline or invasive and seldom display a mixture while borderline and invasive grades often intermingle within other histologic types, especially the mucinous tumors. Based on this tendency, only serous borderline tumors were distinguished from invasive cancers when considering odds ratios by histologic type and grade.

Since matching was performed as the most convenient means for selecting controls comparable to cases in age and geographic locale and not as the principal means of controlling for confounding, matching was not preserved in the analysis. We analyzed our data by constructing frequency counts of cases and controls by study variables and by calculating crude odds ratios (OR). We then used unconditional logistic regression to adjust for the matching variables including age (continuous), study site (MA, NH), body mass index (continuous), which might have influenced likelihood of using body powder, and for variables strongly linked to ovarian cancer risk such as parity (0, 1), oral contraceptive use (never or <3 months, ≥3 months) and family history of breast or ovarian cancer (no, yes) and tubal ligation (no, yes). Most analyses were performed by using the SAS system (SAS Institute, Cary, NC). Tests for linear trend were performed using the likelihood ratio test with continuous forms of the talc variables. Frequency counts from studies included in our review of published studies were entered into STATA (College Station, TX) to compute crude and combined odds ratios.

RESULTS

Table I summarizes data regarding how cases and controls differed demographically and by known risk factors for ovarian cancer, how these same variables influenced genital talc exposure among controls and how the association between talc use in the genital area and ovarian cancer varied among strata. Controls were more likely than cases to have gone beyond high school, to have married, to have had children and to have used oral contraceptives. In examining the frequency of talc use among controls, only study location significantly influenced likelihood of genital talc exposure. Women from New Hampshire were less likely to have used talc in the genital area compared to women from Massachusetts. Ovarian cancer cases in almost all strata were more likely to have used powder genitally compared to controls, with corresponding elevated odds ratios. A notable exception was the lack of an association between talc use and ovarian cancer among women who reported having had a tubal ligation.

Table II shows adjusted odds ratios by manner, type and frequency of powder use. A greater percentage of cases had regularly used powder in some manner compared to the controls.

TABLE II – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH TYPES AND FREQUENCY OF POWDER USE

Type of personal use	Cases Number (%)	Controls Number (%)	Adjusted OR[1]	(95% C.I.)
No personal use	312 (55.4)	334 (63.9)	1.0	
Use, non-genital areas	99 (17.6)	94 (18.0)	1.08	(0.77, 1.50)
Use, dusting perineum	71 (12.6)	51 (9.8)	1.45	(0.97, 2.18)
Use, dusting sanitary napkin	20 (3.6)	12 (2.3)	1.45	(0.68, 3.09)
Use, dusting underwear	8 (1.4)	6 (1.2)	1.21	(0.40, 3.64)
Multiple uses genital area	53 (9.4)	26 (5.0)	2.15	(1.30, 3.57)
Genital use				
No personal genital exposure	411 (73.0)	428 (81.8)	1.0	
Any personal genital exposure	152 (27.0)	95 (18.2)	1.60	(1.18, 2.15)
Longest used type of powder[2]				
No genital use	411 (73.4)	428 (81.8)	1.0	
Talc	148 (26.4)	92 (17.6)	1.69	(1.26, 2.27)
Cornstarch	1 (0.2)	3 (0.6)	0.31	(0.03, 3.01)
Husband use[3,1]				
No	291 (87.6)	346 (92.0)	1.0	
Yes	41 (12.4)	30 (8.00)	1.52	(0.92, 2.52)
Frequency of use per month[4]				
<30	64 (11.5)	28 (5.4)	2.21	(1.37, 3.56)
30–39	59 (10.6)	51 (9.8)	1.17	(0.78, 1.76)
40+	23 (9.8)	15 (2.9)	1.57	(0.80, 3.10)

[1]Adjusted for age (continuous), study center (MA, NH), tubal ligation (ever, never), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months), and primary relative with breast or ovarian cancer (yes, no) and other categories of genital talc use, except where noted.–[2]Adjusted for age (continuous), study center (MA, NH), and tubal ligation (ever, never) and other powder.–[3]Among married women with no personal genital talc use.–[4]Total of all uses in the genital area.

Relative to those with no use of a body powder, those who used powder only in non-genital areas did not have an increased risk of ovarian cancer [OR=1.08 (0.77 and 1.50)]. However, elevated ORs and (95% CI) were observed for women who directly powdered the genital or rectal area [1.45 (0.97 and 2.18)]; who dusted sanitary napkins: 1.45 (0.68 and 3.09); who dusted underwear [1.21 (0.40 and 3.64)] and who used powder in multiple ways in the genital area [2.15 (1.30 and 3.57)]. There was a significant excess of cases who regularly used powder in some manner in the genital area, and the adjusted OR was similar whether the non exposed referent group was considered to be women with no use of talc anywhere [OR= 1.58, (1.16 and 2.16)] or women with no genital use including those who used it as a body powder in non-genital areas [OR= 1.60 (1.18 and 2.15)]. Few of the women in our study reported use of cornstarch rather than a talc-based powder leading to an imprecise and non-significant OR for ovarian cancer risk associated with its use in the genital area. Among married women who never personally used talc in the genital area, there was an increase of borderline significance in ovarian cancer risk for women whose husbands had used talc in their genital area [OR=1.52 (0.92, 2.52)]. When we examined all methods of genital talc use (except exposure from a husband), we found that most of those who used talc had 30 or more applications per month, but there was no apparent trend for increasing risk for ovarian cancer with increasing number of monthly applications.

Table III examines risk for ovarian cancer associated with ordinal categories related to duration or intensity of talc exposure in the genital area relative to women who never used talc or who used it only in non-genital areas. No clear linear trend was apparent in ORs for categories of age at first use, years of use or total applications. To examine dose response, each of these variables was used as a continuous variable in multivariate models. Linear trends were significant only in those models that included women who were not exposed. To duplicate an analysis performed in a previous report (Harlow *et al.*, 1992), we examined total applications censored by excluding use after closure of the female tract or during non-ovulatory years. Although the ORs for the categories displayed a trend, once again only the multivariate model including the non-genitally exposed revealed a significant trend.

Table IV presents a more detailed analysis of the effect of genital use of talc in women who had no pregnancies at all, in women who had a pregnancy not resulting in a liveborn and in women with a liveborn pregnancy. In the latter 2 groups, we examined risk for ovarian cancer with the timing of talc use in relation to the first pregnancy. Genital talc use that began after a first pregnancy appeared to be associated with lower risk compared to use which began before the first pregnancy. The effect was more apparent among those with a liveborn. Eighty-five of 374 parous cases used at least some talc prior to their first liveborn compared to 64 of 416 parous controls, leading to an adjusted OR (95% CI) of 1.58 (1.10 and 2.29). In contrast, 8 of 378 parous cases used talc only after their first livebirth compared to 10 of 417 parous controls, leading to an adjusted OR(95% CI) of 0.97 (0.38 and 2.50) for ovarian cancer associated with talc use after a first livebirth.

Table V shows the average age and use of genital talc for all controls and for cases by histologic type of ovarian cancer. Average age differed by histologic type but did not account for the differences in ORs. The odd ratio for genital talc use was greatest (and significant) for invasive serous tumors and less than 1 only for mucinous tumors (invasive and borderline combined) after adjustment for age and other covariates.

DISCUSSION

Consistent with four recent case-control studies of ovarian cancer (Purdie *et al.*, 1995, Sushan *et al.*, 1996, Cook *et al.*, 1997, Chang and Risch, 1997), our results demonstrate a significant association between the use of talc in genital hygiene and risk for ovarian cancer. In our discussion, we will examine whether this association satisfies traditional criteria for a causal association including consistency and strength of the association, potential biases, dose response and biological credibility.

Figure 1 summarizes data on risk for ovarian cancer with any genital use of talc from 14 case-control studies including this one. The combined odds ratio and 95% CI is 1.36 (1.24 and 1.49), which is statistically significant. Odds ratios deviating most from the pooled value were observed in the smaller studies, and the test for heterogeneity was not significant ($p=0.085$). Thus, the criteria for

TABLE III – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH GENITAL USE OF TALC

Type of exposure	Cases Number (%)	Controls Number (%)	Adjusted OR[1]	(95% C.I.)
No genital use	411 (73.0)	428 (81.8)	1.0	
Age at first use				
<20	97 (17.4)	67 (12.8)	1.46	(1.03, 2.07)
20–25	36 (6.5)	18 (3.4)	1.87	(1.03, 3.39)
>25	13 (2.3)	9 (1.7)	1.54	(0.64, 3.72)
p-value for linear trend is 0.504 excluding non-exposed.				
Years of use				
<20	55 (9.9)	31 (5.9)	1.86	(1.16, 3.00)
20–30	32 (5.8)	26 (5.0)	1.33	(0.76, 2.30)
>30	59 (10.6)	37 (7.1)	1.44	(0.91, 2.26)
p-value for linear trend is 0.477 excluding non-genitally exposed and 0.062 including non-genitally exposed.				
Total applications				
<3000	51 (9.2)	27 (5.2)	1.84	(1.12, 3.03)
3000–10,000	36 (6.5)	28 (5.4)	1.43	(0.84, 2.41)
>10,000	59 (10.6)	39 (7.5)	1.43	(0.92, 2.22)
p-value for linear trend is 0.164 excluding non-genitally exposed and 0.472 including non-genitally exposed.				
Applications censored[2]				
<3000	59 (10.6)	41 (7.8)	1.54	(1.01, 2.35)
3000–10,000	51 (9.2)	31 (5.9)	1.72	(1.08, 2.76)
>10,000	36 (6.5)	20 (3.8)	1.80	(1.02, 3.18)
p-value for linear trend is 0.675 excluding non-genitally exposed and 0.022 including non-genitally exposed.				

[1]Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no), parity (0, ≥1), OC use (<3 months, ≥3 months), tubal ligation, and other categories of genital talc use, except where noted.–[2]Excludes applications following hysterectomy or tubal ligation and applications during pregnancy and periods of OC use. Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).

TABLE IV – EVER USE OF TALC IN THE GENITAL AREA IN RELATION TO PREGNANCY AND CHILDBIRTH

Group	Cases Total	Cases Number exposed	Cases (%) exposed	Controls Total	Controls Number exposed	Controls (%) exposed	Adjusted OR	95% C.I.
Nulligravid[1]	145	42	(29.0)	82	17	(20.7)	1.48	(0.76, 2.86)
Nulliparous[1] prior to first pregnancy	40	13	(32.5)	24	3	(12.5)	2.80	(0.64, 12.20)
Nulliparous[1] only after first pregnancy	40	2	(5.0)	24	1	(4.2)	1.24	(0.10, 15.32)
Parous[1] prior to first livebirth	374	85	(22.7)	416	64	(15.4)	1.58	(1.10, 2.29)
Parous[2] only after first livebirth	378	8	(2.12)	417	10	(2.40)	0.97	(0.38, 2.50)

[1]Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).–[2]Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no) and tubal ligation.

TABLE V – HISTORY OF GENITAL TALC USE AND ASSOCIATED ODDS RATIOS BY HISTOLOGIC TYPE AND GRADE

Histologic type/grade	Total	Average age	Any use of genital talc	No use of genital talc	Adjusted OR[1]	(95% CI)
Controls	523	49.3	95	428	1.0	
Histologic type/grade						
Serous borderline	86	41.8	23	63	1.38	(0.82, 2.31)
Serous invasive	229	54.5	72	157	1.70	(1.22, 2.39)
Mucinous	83	46.7	16	67	0.79	(0.44, 1.40)
Endometrioid/clear cell	130	53.9	31	99	1.04	(0.67, 1.61)
Undifferentiated	35	52.9	10	25	1.44	(0.67, 3.08)

[1]Adjusted for age (continuous), study center (MA, NH), primary relative with breast or ovarian cancer (yes, no), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months) and tubal ligation (ever, never).

consistency of the association appear to be satisfied. A summary odds ratio of 1.36 suggests that between 10 and 11% of ovarian cancers in these populations are attributable to the genital use of talc depending upon whether the average control exposure of 36% or average case exposure of 43% is considered.

Despite the consistency noted above, the relatively weak odds ratios observed could reflect potential biases, especially recall and confounding. Recall bias is possible because talc exposure in these studies is based on personal recollection. However, recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias. Furthermore, if publicity regarding the association correlated with selective recall, one might expect a trend for cases from more recent studies to report higher

Risk of ovarian cancer with perineal exposure to talc from key epidemiologic studies.

Author	Cases Total n	Cases Exposed (%)	Controls Total n	Controls Exposed (%)	Crude OR (95% CI)
Cramer *et al.* (1982)	215	(42.8)	215	(28.4)	1.9 (1.3-2.8)
Hartge *et al.* (1983)	135	(49.6)	171	(58.5)	0.7 (0.4-1.1)
Whittemore *et al.* (1988)	188	(32.1)	539	(46.0)	1.3 (0.9-1.8)
Harlow and Weiss (1989)	116	(42.2)	158	(40.5)	1.1 (0.7-1.7)
Booth *et al.* (1989)	217	(65.0)	434	(59.0)	1.3 (0.9-1.8)
Harlow *et al.* (1992)	235	(48.5)	239	(39.3)	1.4 (1.0-2.1)
Rosenblatt *et al.* (1992)	77	(87.0)	46	(88.0)	1.0 (0.3-3.0)
Chen *et al.* (1992)	112	(6.2)	224	(2.2)	2.9 (0.9-9.4)
Tzonou *et al.* (1993)	189	(3.2)	200	(3.5)	0.9 (0.3-2.7)
Purdie *et al.* (1995)	824	(56.7)	860	(52.0)	1.2 (1.0-1.5)
Shushan *et al.* (1996)	200	(10.5)	408	(5.6)	2.0 (1.0-3.6)
Cook *et al.* (1997)	313	(50.8)	422	(39.3)	1.6 (1.2-2.1)
Chang and Risch (1997)	450	(44.0)	564	(35.6)	1.4 (1.1-1.8)
Cramer *et al.* (1999)	563	(27.0)	528	(18.2)	1.7 (1.2-2.2)
Summary odds ratio (95% confidence interval)					1.4 (1.2-1.5)

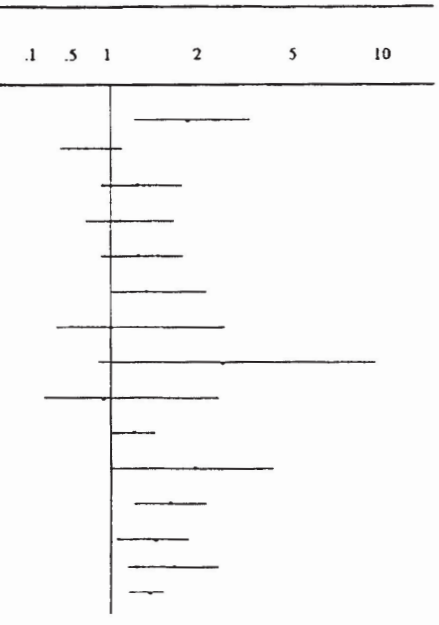

FIGURE 1 – Exposure rates, crude odds ratios and confidence intervals for case-control studies of genital talc use and ovarian cancer.

exposure rates, but the exposure rates noted in Figure 1 do not suggest this is the case. It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer which appears not to be the case from Table V. Our study found the greatest risk to be associated with invasive serous tumors, OR=1.70 (1.22 and 2.39). Cook *et al.* (1997) found talc use to be most strongly associated with serous and unclassified cancers, although Chang and Risch (1997) found endometrioid cancers to be more strongly linked with talc use.

Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or OC use and little variability of the association by these and other variables (Table II). Chang and Risch (1997) adjusted for age, parity, breastfeeding, oral contraceptive use, tubal ligation or hysterectomy and family history and also found the association to persist. Characteristics such as body odor or excessive perspiration might represent subtle constitutional features that might predispose to both talc use and ovarian cancer, but adjusting for BMI should control for these effects. In addition, 2 previous studies (Cook *et al.*, 1997; Chang and Risch, 1997), and our current study found no evidence of elevated risk associated with genital use of a cornstarch based-powder, although in all of these studies the exposure was infrequent and the OR and confidence interval was wide. Further studies would be valuable since this observation suggests that type of powder used may be more important than underlying reason for use.

The most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response. Most talc and ovarian cancer studies that have addressed dose response, including this one, have failed to demonstrate consistent dose response relationships with measures of the intensity of the exposure, especially when the trend is examined among users only. In attempting to address this weakness, we point out that it is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an "application of talc." Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open. There is evidence from several studies that the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (Harlow *et al.*, 1992; Chang and Risch, 1997; Green *et al.*, 1997). We have also proposed that talc use during periods of ovulation may carry greater risk, based on the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusion cysts that form with ovulation.

Our current study also suggests that a term pregnancy may affect the relationship between talc and ovarian cancer in a manner that may be independent of ovulation. We observed that the association between talc and ovarian cancer was more apparent in women who used talc prior to a first liveborn pregnancy compared to those who used it only after a first liveborn pregnancy. This may suggest that ovarian tissue that has not (yet) gone through a pregnancy may be more susceptible to talc-induced damage than tissue that has undergone a pregnancy. A possible biologic explanation for this may involve an ovarian change, known as decidual reaction, that occurs during pregnancy. The decidual reaction refers to differentiation of stromal cells that occurs primarily in the endometrium of the pregnant uterus but which also may be seen in the fallopian tubes, pelvic peritoneum and ovarian surface (Herr *et al.*, 1978). Studies to determine whether the decidual reaction alters the susceptibility of ovaries (or pelvic peritoneum) to talc-induced damage may be informative.

Although we do not know precisely how use of talc in the genital area might induce ovarian cancer, some key elements supporting the biologic plausibility of the association have been established. It has been demonstrated that inert particles contaminating the vagina can reach the ovaries (Venter and Iturralde, 1979). Talc has been found in both normal and malignant ovarian tissue (Henderson *et al.*, 1979), although Heller *et al.* (1996) reported a poor correlation between the amount of talc in the ovaries and personal history of talc use. The patency of the female tract and the nature of ovarian cancer as a surface epithelial (mesothelial) lesion make the ovary a target for foreign body carcinogenesis. Indeed, human ovarian cancer has been demonstrated to be a consequence of occupational asbestos exposure (Keal, 1960). Talc, as a chemical relative of asbestos, appears able to induce histologic changes that are similar to those of asbestos, at least in the lungs (Kleinfeld et al., 1967). Biologic credibility for an association would be strengthened by an animal model, but an experiment capturing all of the potential factors in the human "model" would be very difficult. These elements include chronicity of the exposure, anatomic and physiologic uniqueness of women, effects of pregnancy and potential spread through coitus (as suggested by our finding related to ovarian cancer risk associated with a husband's use of talc). Rodent models seem poorly suited to address these issues because of their infrequent ovulation and the fact that the rodent ovary is encased in a bursal sac.

In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding. The dose-response relationship is weak but improved by considering factors such as closure of the female tract, ovulation and exposure prior to pregnancy, and we have outlined a plausible biologic rationale for this association. We estimate that avoidance of talc in genital hygiene might reduce the occurrence of a highly lethal form of cancer by at least 10%. Balanced against what are primarily aesthetic reasons for using talc in genital hygiene, the risk benefit decision is not complex. Appropriate warnings should be provided to women about the potential risks of regular use of talc in the genital area.

REFERENCES

Booth, M., Beral, V. and Smith, P., Risk factors for ovarian cancer: a case-control study. *Brit. J. Cancer,* **60**, 592–598 (1989).

Chang, S. and Risch, H., Perineal talc exposure and risk of ovarian carcinoma. *Cancer*, **79**, 2396–2401 (1997).

Chen, Y., Wu, P.C., Lang, J.H., Ge, W.Y., Hartge, P. and Brinton, L.A., Risk factors for epithelial ovarian cancer in Bejing, China. *Int. J. Epidemiol.*, **21**, 23–29 (1992).

Cook, L.S., Kamb, M.L. and Weiss, N.S., Perineal powder exposure and the risk of ovarian cancer. *Amer. J. Epidemiol.*, **145**, 459–465 (1997).

Cramer, D.W., Welch, W.R., Scully, R.E. and Wojciechowski, C.A., Ovarian cancer and talc. *Cancer,* **50**, 372–376 (1982).

Green, A., Purdie, D., Bain, C., Siskind, V., Russell, P., Quinn, M., Ward, B. and Survey of Women's Health Study Group, Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. *Int. J. Cancer,* **71**, 948–951 (1997).

Harlow, B.L., Cramer, D.W., Bell, D.A. and Welch, W.R., Perineal exposure to talc and ovarian cancer risk. *Obstet. Gynecol.*, **80**, 19–26 (1992).

Harlow, B.L. and Weiss, N.S., A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc. *Amer. J. Epidemiol.*, **130**, 390–394 (1989).

Hartge, P., Hoover, R., Lesher, L.P. and Mcgowan, L., Talc and ovarian cancer (letter). *J. Amer. Med. Ass.*, **250**, 1844 (1983).

Heller, D.S., Westhoff, C., Gordon, R.E. and Katz, N., The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Amer. J. Obstet. Gynecol.*, **174**, 1507–1510 (1996).

Henderson, W., Hamilton, T. and Griffith, K., Talc in normal and malignant ovarian tissue. *Lancet,* **5**, 449 (1979).

Herr, J.C., Heidger, P.M., Scott, J.R., Anderson, J.W., Curet, L.B. and Mossman, H.W., Decidual cells in the human ovary at term I. Incidence, gross anatomy and ultrastructural features of merocrine secretion. *Amer. J. Anat.*, **152**, 7–28 (1978).

Keal, E.E., Asbestosis and abdominal neoplasms. *Lancet,* **2**: 1211–1216 (1960).

Kleinfeld, Messite, J., Kooyman, O. and Zaki, M.H., Mortality among talc miners and millers in New York State. *Arch Environ. Health,* **14**, 663–667 (1967).

Purdie, D., Green, A., Bain, C., Siskind, V., Ward, B., Hacker, N., Quinn, M., Wright, G., Russell, P. and Susil, B., Reproductive and other factors and risk of epithelial ovarian cancer; an Australian case-control study. *Int. J. Cancer,* **6**, 678–684 (1995).

Rosenblatt, K.A., Szklo, M. and Rosenshein, N.B., Mineral fiber exposure and the development of ovarian cancer. *Gynecol. Oncol.*, **45**, 20–25 (1992).

Shushan, A., Paltiel, O., Iscovich, J., Elchalkal, U., Peretz, T. and Schenker, J.G., Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil. Steril.*, **65**, 13–18 (1996).

Tzonou, A., Polychronopoulou, A., Hsieh, C.C., Rebelakos, A., Karakatsani, A. and Trichopoulos, D., Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int. J. Cancer*, **55**, 508–510 (1993).

Venter, P.F. and Iturralde, M., Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S. Afr. med J.*, **55**, 917–209 (1979).

Whittemore, A.S., Wu, M.L., Paffenbarger, R.S., Sarles, D.L., Kambert, J.B., Grosser, S., Jung, D.L., Ballen, S. and Hendrickson, M., Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder tobacco, alcohol, and coffee. *Amer. J. Epidemiol.*, **128**, 1228–40 (1988).

Young, R.H., Clement, P.B. and Scully, R.E., The Ovary (chapter 53). *In* Sternberg, S.S. (ed.), *Diagnostic Surgical Pathology* (2nd Ed.), p. 2213, Raven Press, New York (1994).